COMPOSITION FOR LOCAL APPLICATION WITH IMPROVED PERCUTANEOUSDRUG RELEASE BY MENTHOL

Patent number:	JP60152413
Publication date:	1985-08-10
Inventor:	ANDORIYUU JIYOOJI TSUUKU
Applicant:	AMERICAN HOME PROD
Classification:	
- international:	A61K9/02; A61K9/06; A61K9/10; A61K9/70; A61K47/00
- european:	A61K9/70E; A61K47/10
Application number:	JP19840267294 19841217
Priority number(s):	US19830564654 19831222

Also published as:

EP0147146 (A:
EP0147146 (A:
GR81250 (B)
DK626384 (L)

Report a data error he

Abstract not available for JP60152413
Abstract of corresponding document: **EP0147146**

Disclosed herein are compositions, products and methods for enhancing the transdermal delivery of physiologically active agents across mammalian skin or membranes and which comprise a percutaneous transfer enhancing amount of menthol and a drug.

COMPOSITION FOR LOCAL APPLICATION WITH IMPROVED PERCUTANEOUSDRUG RELEASE BY MENTHOL

Description of corresponding document: **EP0147146**

The development of new or improved dosage forms and delivery means for physiologically active agents has been and will continue to be the subject of research for both existing and novel drugs. In too many instances a particular drug dosage provides for more drug than is actually required to produce an efficacious and safe therapeutic blood level free from side effects. The reasons for such theoretically excessive doses are many and include, inter alia, the mode of administration, the metabolism of the drug in the gastrointestinal tract, the absolute absorbtion (bioavailability) of the drugs and the situs of absorption. In another aspect the use of sustained release dosage forms and delivery means has increased to further both patient compliance and convenience.

More recently, investigations respecting transdermal drug delivery systems have increased resulting in a number of commercially available products especially for the administration of nitroglycerine. These latter systems apparently provide the advantages inherent in sustained delivery dosage forms and avoid the problems of adrums rapid metabolism upon oral administration.

At the same timegess drug, although equally efficacious therapeutically to a greater amount orally administered, is ingested or absorbed by the patient.

Nevertheless, thefeasibllity,-the suceess and potential of such transdermal systems have heretofore been limited to drugs that are efficacious at lower dose levels and/or have relatively limited water solubility. The explanation for such limitations arise from the formidable barrier provided by the external layer(s) of animal skin and membrane tissues and the limited body areas which are usefully available for application of such transdermal dosage forms.

Various efforts have been pursued- to expand the availability of transdermal delivery to more drugs and overcome the barrier presented by animal skin and membrane. Most such efforts, at least those employing transdermal drug delivery devices, have concentrated on increasing the diffusion of the drug from the device into and through the aforementioned barriers. Other efforts have been more specifically targeted at improving the permeability characteristics or percutaneous absorption capacity of the barrier itself. While some of these latter efforts have reportedly shown some success, the agents employed frequently have caused undesirable systemic side effects as well as tissue damage and irritation at the situs of application.

Agents reported to act as penetration enhancers for transdermal drug delivery include dimethylsulfoxide, disclosed in US. Patent 3,551,554; combinations of sucrose fatty acid esters with a sulfoxide or phosphoric oxide, disclosed in U.S. Patents 3,896,238; 3,952,099 and 4,046,886; and the 1substituted azacycloalkan-2-ones which are the subject ofUS. Patents 3,989,816; 4,316,893 and 4,405,616.

The present invention relates to compositions useful for the transdermal delivery of physiologically active agents to mammals. More particularly, this invention relates to compositions and methods which enhance the percutaneous transfer of topically applied, systemically active drugs and particularly such drugs which have aqueous solubility or which can be made water soluble by the use of derivatives, or in composition, through selection of appropriatepil , buffers, solvents and excipients. Thus the composition of this invention comprises at least one systemically active, water soluble or solubilizable drug, a percutaneous transfer enhancing amount of menthol and a pharmaceutically acceptable vehicle in which the menthol is soluble.

In a further aspect, the invention relates to a method for enhancing the transfer of physiologically active agents into and through mammalian skin and membranes. The method comprises topically applying or administering to substantially the same section of the mammalian skin or membrane an effective amount of a systemically active, water soluble or solubilizable drug, a percutaneous transfer enhancing amount of menthol and a pharmaceutically acceptable vehicle.

Still a further embodiment of this invention resides in a unit dosage form for transdermal delivery of physiologically active agents to mammals. The dosage form comprises an effective amount of a systemically active, water soluble or solubilizable drug comprised within at least one drug reservoir means; a percutaneous transfer enhancing amount of menthol comprised within menthol delivery means; menthol solubilizing means and securing means for attaching the dosage form to a mammal.

Menthol is a secondary alcohol obtained naturally from peppermint or other mint oils or prepared synthetically.

Menthol has many uses as an ingredient in various medicinal preparations due to its analgesic, local anaesthetic and counter irritant properties. It has now been found that menthol acts to enhance the percutaneous transfer of systemically active drugs in mammal.

Thus, this invention provides a topical composition for the transdermal delivery of physiologically active agents to mammals, said composition comprising an effective amount of a systemically active, water soluble or solubilizable drug, a percutaneous transfer enhancing amount of menthol and a pharmaceutically acceptable vehicle comprising at least one pharmaceutically acceptable solvent or solubilizer for said menthol.

This invention also comprises a product for topical use containing an effective amount of a systemically active, water soluble or solubilizable drug useful in medicinal therapy, a percutaneous transfer enhancing amount of menthol and a pharmaceutically acceptable vehicle comprising at least one pharmaceutically acceptable solvent or solubilizer for said menthol, as a combined preparation for sequential in any order or simultaneous use in said therapy.

In this invention the effective amount of drug will mean that amount of drug needed to produce a therapeutic dose following its transdermal administration. That amount will vary, depending, among other factors, on the physiological effect desired, the frequency of administration, drug and intradermal metabolism, drughal-f-life and the amount of menthol and perhaps other percutaneous transfer enhancers employed in the composition.

As stated, a percutaneous transfer enhancing amount of menthol is comprised in the composition. This amount for most drugs, generally ranges from about 4 to about 16 per cent by weight of the composition.

The composition of the invention will further include a pharmaceutically acceptable vehicle containing at least one pharmaceutically acceptable solvent or solubilizer for said menthol. The vehicle in preferred compositions will also contain at least one pharmaceutically acceptable solvent which is a solvent or solubilizer for the drug. The respective solvents or solubilizers for the drug and menthol of this invention may be the same or different. In either case it is preferable thatthe solvents or solubilizers for each the drug and menthol, in the amounts employed, are at least partially soluble or miscible with each other. Most preferably, the solvents or solubilizers for each the drug and the menthol will, in the amounts employed, be wholly soluble or miscible with each other. The pharmaceutically acceptable vehicle may also contain other pharmaceutically acceptable excipients useful for formulating topical pharmaceutical compositions including buffers, neutralizing agents, pH modifiers, viscosity building or controlling agents, gel forming agents, emulsifiers, surfactants, polymers and the like.

Examples of solvents or solubilizers which may comprise the pharmaceutically acceptable vehicle of this invention include one or more of materials such as glycerin, propylene glycol, isopropanol, ethanol, a variety of polyethylene glycols, block copolymers of ethylene glycol and propyleneglyeol, acetylated monoglycerides, lanolin, mineral oil, water, aqueous buffers and the like.

The composition of this invention for application to mammalian skin or membrane may take various forms including creams, lotions, gels, ointments, suppositories, sprays, aerosols and the like.

In another embodiment, the invention includes a method for treating mammals in need of treatment with systemically active agents by the transdermal administration of said agents sequentially or in combination with a percutaneous transfer enhancing amount of menthoL The method is effected by topically administering to substantially the same section of mammalian skin or membrane an effective amount of a systemically active, water soluble or solubilizable drug, a percutaneous transfer enhancing amount of menthol and a pharmaceutically acceptable vehicle. Thus, the method of the invention may also be employed as referred to hereinabove in a method for enhancing the transfer of physiologically active agents through mammalian skin and membranes.In either event the method may be realized through administration of the composition of the invention, a unit transdermal dosage form comprising the composition of the invention, or through sequential administration of the percutaneous transfer agent and drug of this invention via direct application to said mammal or via the unit transdermal dosage form of this invention comprising the same or different means for delivery of each of said percutaneous transfer agent and said drug.

The unit dosage form of this invention as hereinbefore described comprises an effective amount of a systemically active water soluble or solubilizable drug comprised within at least one drug reservoir means.

Said drug reservoir means may take various forms such as pads or sponges impregnated with drug, a polymeric matrixcontainingxthe drug or composition of the drug, a gel formulation (or other formulation having some structural integrity) of the drug, a composition or solution of the drug within a walled container permeable to the drug and available to the skin or membrane of the mammal, a multiplicity of distinct microreservoir compartments containing the drug or drug composition within or homogenously throughout each microreservoir, layers of reservoirs and multiple variants of any of these enumerated and other drug reservoir presentations.

The unit dosage form, as with the other embodiments of this invention, further comprises a percutaneous transfer enhancing amount of menthol. In the unit dosage form, the menthol will be comprised within menthol delivery means which means can be selected from any of the described drug reservoir means, distinct menthol reservoir means and integral menthol reservoir means. Integral menthol reservoir means is defined to include the provision of the menthol together with the securing means, as for example in an adhesive layer.

Menthol solubilizing means and securingmeans for attaching or maintaining contact of the dosage form to a mammal are also comprised by the unit dosage form of the invention The menthol solubilizing means comprise a pharmaceutically acceptable vehicle in which the menthol is soluble or solubilizable and which further is also either a solvent for the drug or is miscible with the drug or drug composition.Thus the menthol solubilizing means may be formulated with any of the menthol, the drug and/or in a distinct reservoir or depot within the unit dosage of the invention, so long as the menthol is soluble or made soluble therein and the drug or drug composition is soluble or miscible therewith prior to transfer through the skin or membrane of the mammaL The securing means will be selected from adhesives, belts such as those with "velcro" fittings, elastic bands or such other devices which are capable of securely attaching the unit dosage to the mammalian subject.

The invention is further illustrated by the following examples.

In examples 1-4; in-vitro percutaneous transfer tests with nude mouse skins were performed as follows; A piece of freshly excised nude mouse skin was mounted across a 6 cm2 opening of a diffusion cell. The test formulation was first impregnated intolynch diameter circles of a thin non-woven rayon fabric usually in amounts representing about 20 mg or more percm2 of skin. The impregnated fabric was applied to the outside or epidermal side of the skin while the inside or tissue side of the skin was exposed to an aerated and stirred volume of Ringer's injection fluid maintained at about 370C. Samples were taken at intervals from the stirred solution and assayed for drug content. The calculated total amount of percutaneously transferred drug is expressed as mg drug per cm2 of exposed skin.

Example 1
The following formulations containing propranolol hydrochloride were prepared: percent by weight

	A	B
Propranolol hydrochloride	55.6	29.6
Glycerol	26.6	47.8
Propylene glycol	8.1	
Menthol	17.8	
n-Decylm ethylsulfoxide	-	3.8
sucrose stearate		10.7

The formulation A mixture became a clear homogenous liquid upon heating but solidified amidst crystallization upon cooling. Formulation B was prepared according to methods described inU8. Patents 3,952,099 and 4,046,886. Two circles ofnonwoven fabric were impregnated with each formulation (designated Al, A2 and B1,B2 respectively) and tested for percutaneous drug transfer across nude mouse skin.

	Al	A2	B1	B2
Amount of drug present in formulation applied to epidermal surface (mg/cm2)	10.95	8.83	5.17	5.83
Amount of drug passing across skin (mg/cm2) after				
2 hours	0.01	0.003	0.004	0.005
4 hours	1.05	0.20	0.02	0.03
6 hours	1.49	0.91	0.06	0.06
9 hours	8.27	2.83	0.18	0.12
12 hours	8.83	3.48	0.37	0.18
22 hours	9.20	4.93	1.31	0.50

The menthol formulation caused much higher transfer than the reference formulation. The differenee was larger than theskitto skin variation seen in the duplicate runs.

Example 2
Formulations containing conjugated estrogens were prepared. A purified and dried concentrate of Conjugated Equine Estrogens was used, which contained per gram, 324 mg of conjugated estrogens

when assayed according to the methods specified in the XX. edition of the U.S. Pharmacopeia. The major components of this mixture of natural estrogens are sodium estrone sulfate (about 54%), sodium equilin sulfate (about 29%), and sodium dihydroequilin sulfate (about 13%). The formulation ingredients, as given below in percentages by weight, were combined, then warmed and stirred to give hazy amber solutions.

Formulation C D E
Dried concentrate of Conjugated Estrogens 4.1 4.1 5.0
Propylene glycol 64.3 64.1 64.9
Isopropanol 16.1 12.0 8.1
Water 15.5 15.8 13.9
Menthol 0 4.0 8.1
Two circles of nonwoven fabric were impregnated with each formulation, so as to contain 2-3 mg of conjugated estrogens. These were applied to nude mouse skins (6 cm2 exposed surface) for transdermal penetration tests. The average of duplicate tests is given below, in units ofyg of transferred estrogen per cm2 of exposed skin surface.

C D E
Sodium estrone sulfate(llg/cm2) passingacross skin after
2 hours 0 0 2
4 hours 0 1 32
6 hours 0 7 101
13 hours 0 46 164
22 hours 0 99 223
C D E
Sodium equilin sulfate (pg/cm2) passing across skin after
2 hours 0 0 0.6
4 hours 0 0.2 13
6 hours 0 3 44
13 hours 0 19 84
22 hours 0 44 103Sodium dihydroequilin sulfate (z g/cm2) passing across skin after
2 hours 0 0 0.3
4 hours 0 0.2 7
6 hours 0 2 25
13 hours 0 11 45
22 hours 0 28 62
The formulation without menthol did not allow. the passage of detectable amounts of estrogen across the skin. The two menthol containing formulations, however, caused the transfer of large amounts of estrogens.All three of the major constituents penetrated the skin, in proportions essentially equal tothegoriginal mixture composition.

Example 3
Formulations containing etodolac,1.8-diethyl-1,3 ,4 ,9- tetrahydropyrano[3,4-t3 indolel-acetic acid, anonsteroidal antiinflammatory, analgesic agent were prepared with and without 5% menthol in aglyceroVpropylene glycol vehicle. The agent, sparingly soluble in water, but solubilized by this vehicle demonstrated about a three fold increase in percutaneous transfer in the presence of menthoL In other experiments, wherein the aqueous solubility of the etodolac were increased via the employment of buffers and/oralkalizing agents the enhancing effect of menthol was even more pronounced in the nude mouse skin studies.

Example 4
Formulation containing 17- B -estradiol (a non-water soluble estrogen) in lipophilic vehicles with and without menthol demonstrated no significant differences in percutaneous transfer. However, when employing 17-ss -estradiol3-sodium sulfate a water soluble derivative of said estrogen in hydrophilic vehicles, formulations containing menthol demonstrated significantly higher flux rates in the nude mouse skin studies.

Example 5
In this experiment the following formulations with and without menthol were evaluated in male albino rats.

weight percent
A B
Propranolol hydrochloride 18.02 17.98
Glycerin 54.10 63.88
Isopropanol 17.84 18.14
Menthol 10.04

The above formulations were impregnated on circular, cotton matrix patches, each patch having a diameter of 3cm and containing 0.3g of test formulation. The patches were applied to a shaved area on the backs of the animals and covered (secured) with adhesive tape. Blood samples were obtained twice (for each rat) from ten rats in each of two treatment groups at different time points.

The results at the indicated time points are as follows, the. plasma level mean at each time point representing the average of two animals

Mean in ng/ml

Time (Hours)	A	B
1	0.8	5.5
2	165.5	
3	140.0	9.5
4	115.59.D	
6	457.0	4.5
8	49 1.0	0.8
12	922.0	4.5
16	1317.0	11.5
24	628.0	6.5
32	73.5	1.8

COMPOSITION FOR LOCAL APPLICATION WITH IMPROVED PERCUTANEOUSDRUG RELEASE BY MENTHOL

Claims of corresponding document: **EP0147146**

CLAIMS 1. A topical composition for the transdermal delivery of physiologically active agents to mammals comprising an effective amount of a systemically active water soluble or solubilizable drug, a percutaneous transfer enhancing amount of menthol and a pharmaceuti cally acceptable vehicle comprising at least one pharmaceutically acceptable solvent or solubilizer for said menthol.

2. A product for topical use containing an effective amount of a systemically active, water soluble or solubilizable drug useful in medicinal therapy, a percutaneous transfer enhancing amount of menthol and a pharmaceutically acceptable vehicle comprising at least one pharmaceutically acceptable solvent or solubilizer for said menthol, as a combined preparation for sequential in any order or simultaneous use in said therapy.

3. A composition or product as claimed in Claim 1 or Claim 2 wherein said menthol comprises by weight about 4% to about 16% of the composition or combination.

4. A composition or product as claimed in any one of Claims 1,2 or 3 in which the pharmaceutically acceptable vehicle further comprises at least one pharmaceutically acceptable solvent for the drug.

5. A composition or product as claimed in Claim 4 in which the solvent for each of the drug and menthol are in the amounts employed at least partially miscible with each other.

6. A composition or product asclaimed in any one of Claims 1 to 3 in which the solvents for each of the drug and menthol are in the amounts employed wholly soluble or miscible with eachpother.

7. A composition or product as claimed in any one of Claims 1 to 6 in which the pharmaceutically acceptable vehicle is selected from one or more of the following glycerin, propylene glycol, isopropanol, ethanol, polyethylene glycol, block copolymer of ethylene glycol and propylene glycol, acetylated monoglyceride, lanolin, mineral oil, water and aqueous buffer.

8. A composition as claimed in any one of Claims 1 to 7 which is in the form of a cream, lotion, gel, ointment, suppository, spray or aerosol.

9. A unit transdermal dosage form for transdermal

delivery of physiologically active agents to mammals comprisinganeffective amount of a ~ ~ systemically active water soluble or solubilizable drug comprised within at least one drug reservoir means; a percutaneous transfer enhancing amount of menthol comprised within menthol delivery means selected from the group consisting of any drug reservoir means, distinct menthol reservoir means, menthol matrix means and adhesive means; menthol solubilizing means and securing means for attaching the dosage form to a mammal.

10. A unit transdermal dosage form as claimed in Claim 9 wherein the drug reservoir means comprises a pad or sponge impregnated with drug, a gel formulation of the drug,a composition or solution of the drug within a walled container permeable to the drug and available to the skin or membrane of the mammal, a multiplicity of distinct microreservoir compartments containing the drug or drug composition within or homo geneously throughout each reservoir.

11. A unit transdermal dosage form as claimed in Claim 9 wherein the menthol delivery means is selected from any of the drug reservoir means of Claim 10.

12. A method for enhancing the transfer of physio logically active agents through mammalian skin and membranes comprising topically administering to substantially the same section of mammalian skin or membrane an effective amount of a systemically active, water soluble or solubilizable drug, a percutaneous transfer enhancing amount of menthol and a pharmaceutically acceptable vehicle.

13. The method of Claim 12 wherein said drug and said percutaneous transfer amount of menthol are supplied to said mammalsequentially -- 14. The method of Claim 12 wherein said drug and said percutaneous transfer amount of menthol are supplied to said mammal simultaneously, 15. The method of Claim 12, 13 or 14 wherein the menthol is soluble in said vehicle, 16. The method of Claim 12, 13 or 14 wherein the menthol is soluble in said vehicle and the drug is at least'partially soluble in said vehicle.

17. The method of Claim 12 wherein each of the drug and the menthol are comprised in separate solubilizing compositions therefor and each of said compositions are substantially miscible with the other of said compositions and wherein at least one of said compositions contains said pharmaceutically acceptable vehicle.

CLAIMS FOR AUSTRIA 1. A process for preparing a topical composition for the transdermal delivery of physiologically active agents to mammals which comprises bringing an effective amount of a systemically active water soluble or solubilizable drug, a percutaneous transfer enhancing amount of menthol and a pharma ceutically acceptable vehicle comprising at least one pharmaceutically acceptable solvent or solub ilizer for said menthol into a form suitable for

therapeutic administration.

2. A process for preparing a product for topical use containing an effective amount of a systemically active, water soluble or solubilizable drug useful in medicinal therapy, a percutaneous transfer enhancing amount of menthol and a pharmaceutically acceptable vehicle comprising at least one pharmaceutically acceptable solvent or solubilizer for said menthol, which comprises formulating said product as a combined preparation for sequential in any order or simultaneous use in said therapy.

3. A process for preparing a composition or product as claimed in Claim 1 or Claim 2 wherein said menthol comprises by weight about 4% to about 168 of the composition or combination.

4. A process for preparing a composition or product as claimed in any one of Claims 1, 2 or 3 in which the pharmaceutically acceptable vehicle further comprises at least one pharmaceutically acceptable solvent for the drug.

5. A process for preparing a composition or product as claimed in Claim 4 in which the solvent for each of the drug and menthol are in the amounts employed at least partially miscible with each other.

6. A process for preparing a composition or product as claimed in any one of Claims 1 to 3 in which the solvents for each of the drug and menthol are in the amounts employed wholly soluble or miscible with each other.

1i- T: 7. A process for preparing a compositiondr product as claimed in any one of Claims 1 to 6 in which the pharmaceutically acceptable vehicle is selected from one or more of the following glycerin, propylene glycol, isopropanol, ethanol, poly ethylene glycol, block copolymer of ethylene glycol and propylene glycol, acetylated monoglyceride, lanolin, mineral oil, water and aqueous buffer.

8. A process'for preparing a composition as claimed in any one of Claims 1 to 7 which is in the form of a cream, lotion, gel, ointment, suppository, spray or aerosol.

9. A process for preparing unit transdermal dosage form for transdermal delivery of physiologically active agents to mammals which comprises bringing an effective amount of a systemically active water soluble or solubilizable drug comprised within at least one drug reservoir means; a percutaneous transfer enhancing amount of menthol comprised within menthol delivery means selected from the group consisting of any drug reservoir means, distinct menthol reservoir means, menthol matrix means and adhesive means; menthol solubilising means and securing means for attaching the dosage form to a mammal into a form suitable for therapeutic administration.

10. A process for preparing a unit transdermal dosage form as claimed in Claim 9 wherein the drug reservoir means comprises a pad or sponge impregnated with drug, a gel formulation of the drug, a composition or solution of the drug within a walled container permeable to the drug and available to the skin or membrane of the mammal, a multiplicity of distinct microreservoir compart ments containing the drug or drug composition within or homogeneously throughout each reservoir.

11. A process forpreparing a unit transdermal dosage form as claimed in Claim 9 wherein the menthol delivery means is selected from any of the drug reservoir means of Claim 10.
